The defence of body weight: a physiological basis for weight regain after weight loss

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Abstract
Although weight loss can usually be achieved by restricting food intake, the majority of dieters regain weight over the long-term. In the hypothalamus, hormonal signals from the gastrointestinal tract, adipose tissue and other peripheral sites are integrated to influence appetite and energy expenditure. Diet-induced weight loss is accompanied by several physiological changes which encourage weight regain, including alterations in energy expenditure, substrate metabolism and hormone pathways involved in appetite regulation, many of which persist beyond the initial weight loss period. Safe effective long-term strategies to overcome these physiological changes are needed to help facilitate maintenance of weight loss. The present review, which focuses on data from human studies, begins with an outline of body weight regulation to provide the context for the subsequent discussion of short- and long-term physiological changes which accompany diet-induced weight loss.

Key words: appetite, diet, hypothalamus, obesity, weight gain, weight loss

INTRODUCTION
Although weight loss can usually be achieved through dietary restriction and/or increased physical activity, the overwhelming majority of people regain the weight that they have lost over the long-term. A meta-analysis concluded that 4.5 years after completing a structured weight-loss programme comprising a hypocaloric diet with or without exercise, the average weight loss maintained was 3 kg (representing a 3.2% reduction in initial weight) [1]. The proportion of people who successfully maintain weight loss varies depending on the definition of ‘weight loss maintenance’ from less than 3% (for maintaining 100% of reduced weight at all annual visits for 4–5 years after completion of a weight-loss programme [2]) to 28% (for maintaining a loss of at least 10% of initial body weight at 4 years [3]). Wing and Hill [4] propose defining successful weight loss maintenance as “intentionally losing at least 10% of initial weight and keeping it off for at least 1 year”. According to this definition, 20.6% of 228 overweight people in a random-digit-dial telephone survey in the U.S.A. reported being successful weight-loss maintainers [4]. Why is diet-induced weight loss so difficult to maintain?

The present review, which focuses on data from human studies, begins with an outline of body weight regulation to provide the context for the subsequent discussion of short- and long-term physiological changes which accompany diet-induced weight loss. A number of comprehensive reviews of the topic which have included insights from animal models of obesity have been published elsewhere [5,6].

BODY WEIGHT REGULATION
Given the considerable variation in food intake from day to day, the body weight of most adults remains remarkably stable over time. Although large weight changes can be brought about in humans and animals through dietary restriction or overfeeding, when free feeding is resumed, body weight and adiposity return accurately to baseline levels [7,8]. This homeostatic regulation of body weight occurs primarily in the hypothalamus, and results from integration of peripheral signals conveying information about both short-term food intake and long-term energy balance. It seems that this system protects us against weight loss more vigorously than from weight gain [9,10], which is clearly beneficial for survival during periods when food is scarce, as it was throughout most of human evolution, and is still in many parts of the world. However, for an obese person living in an...
environment in which high-calorie food is widely available, it means that weight loss achieved through dietary restriction is extremely difficult to maintain.

**Homoeostatic regulation**

The ARC (arcuate nucleus) of the hypothalamus is the primary brain region involved in the homoeostatic control of food intake. Within the ARC are two distinct but interconnected groups of neurons with opposing effects on energy balance. Neurons which co-express NPY (neuropeptide Y) and AgRP (agouti-related peptide) stimulate food intake, whereas neurons expressing POMC (pro-opiomelanocortin) have the opposite effect. Projections from the ARC travel to other hypothalamic regions, including the PVN (paraventricular nucleus) where TRH (thyrotropin-releasing hormone), CRH (corticotrophin-releasing hormone) and oxytocin are produced (hunger-suppressing), and the lateral hypothalamus, which is the source of MCH (melanin-concentrating hormone) and orexins (hunger-stimulating).

Peripheral signals reflecting long- and short-term energy balance are processed centrally to influence the relative activity between the two ARC circuits. The hormones leptin (from adipose tissue) and insulin (from the pancreas) are involved in the long-term regulation of energy balance, whereas short-term signals send information to the brain on a meal-to-meal basis and include hormones from the gastrointestinal tract and pancreas, such as ghrelin, CCK (cholecystokinin), GLP-1 (glucagon-like peptide-1), amylin, PP (pancreatic polypeptide) and PYY (peptide YY), along with several others, including many almost certainly yet to be described (Table 1). This peripheral information is transmitted via the bloodstream and the vagus nerve to the hypothalamus and hindbrain (including the area postrema and the nucleus of the solitary tract). Reciprocal pathways project between these areas, allowing integration of signals to regulate food intake and energy expenditure (Figure 1) [12]. The homoeostatic regulation of body weight has been discussed in more detail elsewhere [11].

**Hedonic influence on appetite**

If appetite were controlled solely by homoeostatic mechanisms, we would eat only to meet nutritional requirements, which is clearly not the case. In addition to homoeostatic pathways, the hypothalamus receives inputs from the cortex and reward circuits in the limbic system (‘hedonic’ pathways) related to the sight, smell and taste of food, along with emotional and social factors, which are all integrated to have an impact upon energy intake and expenditure. The hedonic pathways can override the homoeostatic system, increasing the desire to consume palatable energy-dense food even when energy stores and food supply are abundant.

There is evidence of significant interactions between homoeostatic and hedonic pathways of appetite regulation. Leptin has been shown to influence taste and reward pathways [39–41], and ghrelin stimulates the mesolimbic dopaminergic pathway and increases consumption of sweet foods [42,43]. In addition, stimulation of the CB1 (cannabinoid 1) receptor, which is widely distributed in hypothalamic nuclei and brainstem regions known to be crucial in the homoeostatic control of appetite [44], increases not only food intake, but a preference for palatable foods [45], indicating an influence on feeding also via non-homoeostatic reward pathways.

**PHYSIOLOGICAL ADAPTATIONS TO WEIGHT LOSS**

There is accumulating evidence that diet-induced weight loss brings about compensatory changes in several biological pathways involved in the utilization and storage of energy, and the regulation of appetite, which collectively predispose to weight regain (summarized in Table 2). Some of these changes are more pronounced during dynamic weight loss than after stabilization at a reduced body weight. However, recent studies have shown that many of these changes represent not only a transient response to dynamic weight loss, but persist for 1 year or more following initial weight reduction.

**Energy expenditure**

In humans, the three principal components of TEE (total energy expenditure) are REE (resting energy expenditure; comprised of processes such as maintaining transmembrane ion gradients and resting cardiopulmonary activity), TEF (thermic effect of feeding; the energy required to digest, transport and deposit nutrients), and NREE (non-resting energy expenditure; mainly in the form of physical activity). In weight-stable adults, REE, TEF and NREE make up approximately 60, 10 and 30% respectively of TEE [46].

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**Table 1 Peptides and hormones involved in appetite regulation**

<table>
<thead>
<tr>
<th>Location</th>
<th>Anorexigenic</th>
<th>Orexigenic</th>
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<tr>
<td>Hypothalamus</td>
<td>TRH [17]</td>
<td>Orexins [18]</td>
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<tr>
<td>Hypothalamus</td>
<td>CRH [19]</td>
<td>MCH [20]</td>
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<td>Hypothalamus</td>
<td>Oxytocin [21]</td>
<td>Endocannabinoids [22]</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>CCK [27]</td>
<td>Ghrelin [28]</td>
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<td>Gastrointestinal tract</td>
<td>GLP-1 [29]</td>
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<td>Enterostatin [32]</td>
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<td>Bombesin [33]</td>
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<td>Uroguanylin [34]</td>
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<td>Pancreas</td>
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<td>Pancreas</td>
<td>Insulin [36]</td>
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<td>Adipocytes</td>
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<td>Adipocytes</td>
<td>Leptin [38]</td>
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[12]: Sumithran and J. Proietto

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Figure 1  Selected pathways involved in body weight regulation
CART, cocaine- and amphetamine-regulated transcript; αMSH, α-melanocyte-stimulating hormone. This Figure was reproduced from Proietto J. Why is treating obesity so difficult? Justification for the role of bariatric surgery. Med. J. Aust. 2011; 195(3): 144–146. © Copyright 2011 The Medical Journal of Australia – reproduced with permission.

Table 2  Physiological changes after diet-induced weight loss

<table>
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<tr>
<th>Factor</th>
<th>Expected effect</th>
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<tr>
<td>↓Energy expenditure</td>
<td>Increase energy storage</td>
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<tr>
<td>↓Fat oxidation</td>
<td></td>
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<tr>
<td>↓Thyroid hormones</td>
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<tr>
<td>↑Cortisol</td>
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<tr>
<td>↑GIP</td>
<td>Increase food intake</td>
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<tr>
<td>↓Leptin</td>
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<td>↓PYY</td>
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<td>↓Amylin</td>
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<td>↓Insulin</td>
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<td>↑Ghrelin</td>
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<tr>
<td>↑Appetite</td>
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<tr>
<td>Altered neural activation</td>
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<tr>
<td>↑Pancreatic polypeptide</td>
<td>↑Reduce food intake</td>
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Diet-induced loss of 10% of body weight leads to a reduction in TEE to a level 15% below that which can be accounted for by the alterations in body mass and composition, in both lean and obese persons [46]. The degree to which REE actually declines is controversial [47–49]; however, a greater than predicted reduction in NREE accounts for the majority of the decrease in TEE and appears to be largely due to increased efficiency of skeletal muscle, particularly at low workloads [50,51]. This disproportionate decline in TEE has been shown to persist for more than 1 year in subjects who maintain a reduced body weight [52].

Substrate metabolism
Substrate metabolism is heavily dependent on a number of factors, including energy balance (i.e. weight stability compared with dynamic weight change), physical activity and nutritional status (i.e. dietary macronutrient composition, and whether measured in fed or fasted state) [53,54]. Studies in rodent models of diet-induced obesity allow examination of the metabolic state during obesity development, treatment and relapse, which is not feasible in humans. In diet-induced obese rats, dietary energy restriction is accompanied by a reduction in non-protein RQ (respiratory quotient), indicating a preference for the use of lipids over carbohydrates [55]. After maintenance of the reduced weight, fuel utilization shifts to a preference for carbohydrate use, which continues during weight regain [55]. Increased carbohydrate oxidation spares dietary fat for deposition. A number of human studies have also demonstrated that weight-stable formerly obese subjects have lower fasting or 24-h rates of fat oxidation compared with matched control subjects, or an impaired ability to appropriately increase fat oxidation in response to a high-fat diet [56–61]. This may lead to positive fat balance and negative carbohydrate balance [57,60], which has been proposed to stimulate...
feeding to restore glycogen reserves [62]. Longitudinal studies have suggested that a high fasting or 24-h RQ (indicating low fat oxidation) is associated with weight gain over time [63–65]. After cessation of a weight-loss programme, a significant correlation has been shown in weight-stable reduced-obese women between changes in RQ and weight regain during the follow-up period \((r = 0.89, P < 0.01)\) [66]. In contrast with lower basal and 24-h fat oxidation, fat oxidation may be higher during low-level exercise (i.e. exercise commensurate with activities of daily living) following diet-induced weight loss compared with pre-weight loss values [50,67], which is associated with a reduction in the ratio of skeletal muscle glycolytic to fatty acid oxidative enzyme activity [67]. It has been suggested that this may be related to the increase in skeletal muscle efficiency, in that the more metabolically efficient slow-twitch muscle fibres derive a greater proportion of energy from fat oxidation than the primarily glycolytic (and less efficient) fast-twitch fibres, although alterations in fibre type were not demonstrated in skeletal muscle biopsies [67].

**Autonomic nervous system**

Obesity is associated with resting SNS (sympathetic nervous system) overactivity (‘sympathetic overdrive’) [68,69]. There is evidence that this may not only be the result of obesity [66,70–73], but may also be contributing to its development [74,75]. Chronic SNS overactivity may lead to reduced sensitivity or down-regulation of adrenoreceptors [76], and it has been hypothesized that consequent blunting of SNS responsiveness may impair energy expenditure, post-prandial thermogenesis and fat oxidation [77,78]. In obese subjects, diet-induced weight loss has consistently been shown to be accompanied by significant reductions in sympathetic activity and an increase in cardiac parasympathetic function [73,79–81]. The increase in cardiac parasympathetic tone is attenuated during prolonged (≥4 months) weight-loss maintenance and weight regain [81–83], whereas a recent study showed divergent effects of weight-loss maintenance on markers of sympathetic function, with a sustained reduction in whole-body noradrenaline spillover, but a rebound in muscle sympathetic nerve activity, implying either a further reduction in sympathetic outflow in another organ or tissue bed, or a mismatch between sympathetic nerve firing and noradrenaline overflow during weight-loss maintenance [83].

**Hypothalamic–pituitary–thyroid axis**

Under normal circumstances, TRH (thyrotropin-releasing hormone) from the paraventricular nucleus of the hypothalamus stimulates the release of TSH (thyroid-stimulating hormone) from the anterior pituitary, resulting in the production and release of \(T_3\) (thyroxine) and \(T_4\) (3,3′,5-triiodothyronine) by the thyroid gland. \(T_4\) is converted into the more biologically active \(T_3\) in peripheral target tissues. Thyroid hormones play an important role in energy expenditure [84,85]. In adults receiving \(T_4\) replacement for the treatment of hypothyroidism, REE is significantly negatively correlated with TSH and is sensitive to small changes in thyroxine dosage, even when thyroid hormone levels are maintained within the normal range [84]. Some of this increase in REE may be due to mitochondrial uncoupling in skeletal muscle, which has been shown to occur in the presence of increased circulating thyroid hormone levels [86]. The importance of thyroid hormones to adaptive thermogenesis has been demonstrated in thyroidecmetomized rats, which become hypothermic when exposed to cold. \(T_4\) replacement prevents this, unless conversion of \(T_4\) into \(T_3\) in brown adipose tissue is blocked [87]. Energy restriction has generally been found to suppress the hypothalamic–pituitary–thyroid axis, characterized by impaired secretion of TSH in response to TRH, reductions in circulating TSH and \(T_3\) and increased production of the inactive \(rT_3\) (reverse \(T_3\)), with variable effects on total and free \(T_4\) [72,88–93]. Alterations in \(T_3\), \(rT_3\) and \(T_4\) have been described to return towards baseline during maintenance of the reduced weight in some [90,91,94,95], but not all [72,96], studies.

**Hypothalamic–pituitary–adrenal axis**

CRH is released from the PVN in response to stress and acts in the anterior pituitary to stimulate the release of ACTH (adrenocorticotropic hormone), resulting in production of cortisol, mineralocorticoids and androgens from the adrenal glands. Cortisol excess (for example in Cushing’s syndrome) leads to weight gain, particularly central adiposity, and a significant correlation has been reported between increases in appetite and fasting plasma cortisol after a weight-loss programme in obese men and women [97]. A study in rats has demonstrated that cortisol inhibits the suppressive action of leptin on food intake and body weight [98]. Increased circulating cortisol, and reduced dexamethasone suppression or diurnal variation of cortisol production, have been demonstrated [91,99–102], although not consistently [103] in both lean and obese humans following reduction in food intake, particularly with greater degrees of energy restriction. Alterations in cortisol metabolism are reversible upon return to unrestricted feeding [99].

**Appetite-regulating adipocyte and gastrointestinal hormones**

Following weight loss, changes occur in circulating concentrations of a multitude of peripheral hormones involved in appetite regulation. Although there are some inconsistencies, which are likely to be due to considerable heterogeneity in methodology between studies (including participant characteristics, dietary interventions, degree of weight loss, study duration and hormone fragments assayed), the majority of studies have found that diet-induced weight loss is accompanied by hormone changes which collectively promote weight regain and restoration of energy balance.

Leptin acts in the hypothalamus to reduce food intake and increase energy expenditure by reducing the expression of AgRP and NPY, and stimulating that of POMC [104–106]. When individuals are in energy balance at their usual weight, leptin secretion is proportional to fat mass [107]. In keeping with its proposed role as a signal of energy depletion [108], leptin levels decrease profoundly following dietary restriction [109–111] and are significantly lower during dynamic weight loss than during weight-loss maintenance [112]. Administration of leptin to people at their baseline weight has little effect on body weight and appetite [113], whereas leptin administration during an energy deficit reduces appetite [114], and in weight-stable weight-reduced
subjects, leptin ‘replacement’ to pre-weight loss levels reverses many of the adaptive physiological changes involving thyroid hormones, the autonomic nervous system, appetite, energy expenditure, skeletal muscle efficiency and regional brain activation [72,115,116].

Other hormonal perturbations resulting from diet-induced weight loss include increases in circulating ghrelin, GIP (gastric inhibitory polypeptide) and PP and reductions in PYY, CCK, insulin and amylin [59,111,117–122]. GLP-1 secretion has been variably reported to increase, decrease or remain unchanged following weight loss [111,123,124]. All of the abovementioned hormones inhibit food intake [27,29,30,35–37], other than ghrelin, which stimulates hunger [28], and GIP, which may have a role in energy storage [125]. As such, it can be seen that almost all of these changes would be expected to favour regain of lost weight, by increasing hunger, reducing satiety and promoting energy storage.

There is recent evidence that these hormonal changes are not merely a transient response to negative energy balance. In a study conducted by our research group [111], 50 overweight or obese men and women underwent a 10-week very-low-energy diet-based weight-loss programme, followed by a 12 month period during which they attempted to maintain their weight loss. Subjects were required to lose at least 10% of their initial weight and peripheral appetite-mediating hormones were measured in the 34 participants who completed the study at baseline, at the end of the weight loss period and 12 months later. Initial weight loss was (mean ± S.E.M.) 13.5 ± 0.5 kg (14% of baseline weight), and participants maintained a weight reduction of −7.9 ± 1.1 kg at 12 months. Weight loss was accompanied by significant reductions in circulating leptin, PYY, CCK, insulin and amylin, and increases in ghrelin, GIP and PP, which persisted 12 months later, even after the onset of weight regain.

**Subjective appetite**

In keeping with the expected effects of the hormonal adaptations to weight reduction, sustained increases in subjective appetite have been described following diet-induced weight-loss in obese adults [97,111]. Interestingly, there is evidence that dietary weight loss increases not only appetite itself (i.e. increases in hunger, desire to eat and prospective food consumption) [97,111], but also the perceived rewarding properties of food [126] and the preference for high-calorie food. One study compared the taste preferences of normal-weight, obese and formerly obese subjects for liquid solutions with various sugar and fat content. The formerly obese group had previously lost a mean of 31 kg with a low-calorie diet and had been maintaining a loss of at least 13.6 kg for at least 1 year prior to the study. The normal-weight group found a solution containing 20% lipid and <10% sucrose optimal, the obese group preferred a high-fat solution and the formerly obese group preferred solutions high in both fat and sugar [127]. Several studies have reported that changes in appetite after weight loss are related to alterations in circulating leptin [97,110,128].

**Regional brain activation**

Studies using functional brain imaging techniques have provided valuable insight into alterations in brain activity patterns in response to food stimuli in obese subjects after diet-induced weight loss. One study found increased neural activity in the limbic (reward) system and areas involved in executive function and decision-making, whereas reduced activity was seen in the hypothalamus and areas involved in the emotional control of food intake, integrative cognitive control functions and motor planning, compared with baseline in reduced-obese subjects [116]. This may indicate a state of increased responsiveness to food reward with decreased control of food intake. Others have shown that, when presented with food stimuli, reduced-obese individuals have altered activation in several brain areas involved in the control of complex aspects of eating behaviour compared with obese and lean controls, including the insula, inferior visual cortex, posterior cingulate cortex, posterior hippocampus and amygdala [129,130]. In one study, regional cerebral blood flow increased in the middle insula increased in response to tasting a liquid meal in obese and post-obese subjects, but not in lean individuals [130].

In another, activation of the insula and inferior visual cortex in response to images of palatable food compared with non-food images was not as robust in reduced-obese as in lean individuals in the eucaloric state. However, after 2 days of overfeeding, food responses in the insula and hypothalamus were significantly attenuated in the lean, but not reduced-obese, subjects, suggesting a possible impairment in ability to sense a positive energy balance following weight loss [129]. Among other activities, the insula is involved in mediating the desirability of food [131]. Activation in this area in response to images of high-calorie foods is stimulated by ghrelin [132] and attenuated by administration of leptin in reduced-obese or congenitally leptin-deficient adults [116,133].

In a study which compared nine formerly obese people with 20 obese non-dieters, the successful dieters were found to have greater activation in the dorsal prefrontal cortex (an area involved in the cognitive control of behaviour) and less activation in the orbitofrontal cortex (an area involved in determining the reward value of sensory and visceral inputs) after a meal than non-dieters. This pattern of activation was associated with the higher levels of dietary restraint found in the successful dieters [134].

**STRATEGIES FOR SUCCESSFUL WEIGHT LOSS MAINTENANCE**

In the ‘obesogenic’ environment which prevails in most of the developed world, the multitude of physiological adaptations to weight loss which aim to restore body weight are a hindrance to obese dieters, most of whom will regain weight over time. Despite this, there are individuals who manage to maintain significant weight losses over the long-term. Most of the published data regarding these uniquely successful weight loss maintainers comes from the NWCR (National Weight Control Registry), a database of more than 4000 adults in the U.S.A., who have maintained weight losses of at least 13.6 kg (30 lb) for at least 1 year. Members, of whom 97% are Caucasian and 80% women, are recruited via newspaper and magazine advertisements, and data are self-reported [135]. Participants have lost an average of
30 kg, and have maintained the minimum 13.6 kg weight loss for an average of 5.5 years [135], and 83% report a trigger for their weight loss, most commonly a medical or emotional event [136]. Analyses of strategies reported by registry members to maintain weight loss have revealed a number of key behaviours common to the majority of participants. (i) Eating a low-calorie low-fat diet with minimal variation. Participants reported consuming a mean of 1306 (women) to 1685 (men) kcal/day, with <25% of calories coming from fat. This is around 30% less than the energy and fat intakes reported by respondents in the NHANES III (Third National Health and Nutrition Examination Survey) [137]. In addition, the majority of NWCR participants consume a diet with minimal variety in food groups and adhere to this without variation on weekends or holidays. Those who do not are more likely to regain weight [138,139]. (ii) Eating breakfast every day (78%) [136]. (iii) Frequent self-monitoring. 78% of NWCR members weigh themselves at least once a week, and 50% count calories or grams of fat [136]. (iv) Undertaking regular exercise (91%), equivalent to walking 45 km (28 miles)/week or around 1 h/day of moderately intense activity [136]. NWCR members spend more time engaged in physical activity, particularly in high-intensity activity, than people who are stable at their baseline weight, whether lean or obese [136,140]. (v) Limiting television viewing. A total of 62% report watching television for fewer than 10 h/week compared with the national reported U.S.A. average of 28 h [141].

Given that the compensatory adaptations to weight loss lead to a reduction in energy expenditure and increased propensity to fat storage, consistent application of the combination of abovementioned behaviours would seem an ideal way to prevent weight regain after weight loss. However, for any person, long-term rigid adherence to the dietary and exercise strategies described by NWCR participants would be exceedingly difficult, let alone for weight-reduced individuals, in whom appetite has increased, in a setting where they are surrounded by food, particularly if the environment is not conducive to using physical activity as a means of transport. This is highlighted by the fact that even within the successful NWCR group, small weight regains are common and very few individuals reduce their weight again following regain [142].

The durable success of bariatric surgical procedures such as LAGB (laparoscopic adjustable gastric banding) and RYGB (Roux-en-Y gastric bypass) is likely to be related to the fact that appetite is reduced post-operatively, in contrast with the appetite changes which accompany non-surgical methods of weight loss [143,144]. Hormonal adaptations encouraging weight regain are similar following LAGB and diet-induced weight loss, and the mechanism for appetite suppression following LAGB is not fully understood [145]. A hormone profile which favours appetite suppression is seen after RYGB [118,146,147].

**FUTURE DIRECTIONS**

Recent attention has focused on the potential contribution of gut flora to energy absorption and fat deposition, and diet-induced weight loss induces changes in the prevalence of various species of gut micro-organisms [148–151]. Whether this has any role in facilitating weight regain is yet to be determined.

Although evidence of physiological adaptations to weight loss which encourage weight regain continues to accumulate, there are currently no non-surgical treatments available with demonstrated long-term safety and efficacy to circumvent these changes and assist weight-reduced obese people who are unable to maintain weight loss. In recent months, the U.S.A. Food and Drug Administration has approved two appetite-suppressing medications for the treatment of obesity: lorcaserin (a serotonin 2C receptor agonist) and the combination of phentermine and topiramate (Qsymia), although post-marketing studies of long-term cardiovascular safety are required. It seems logical that restoration of appetite-regulating hormones to pre-weight loss values may facilitate weight-loss maintenance and, indeed, many of the biological perturbations which accompany weight loss are attenuated following administration of leptin in doses calculated to replicate pre-weight loss levels [72,115,116,152]. In obese subjects consuming an energy-restricted diet, a combination of analogues of leptin (metreleptin) and amylin (pramlintide) was found to have synergistic effects on weight loss compared with treatment with either alone [153]. However, in 2011, a randomized clinical trial was stopped prematurely due to safety concerns and development of the combination therapy has since been discontinued (Takeda Pharmaceutical Company Ltd press release; http://takeda.com/press/article,42791.html). Other pharmacological agents currently undergoing clinical trials for the treatment of obesity include the GLP-1 analogue liraglutide and the combination of naltrexone and bupropion (Contrave) [154,155]. The growing evidence of sustained physiological adaptations to weight loss which encourage weight regain justifies the long-term use of medications with demonstrated long-term safety and efficacy to suppress appetite and assist with weight-loss maintenance.

**REFERENCES**


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